

Serial No.: 10/044,848
Group Art Unit No.: 1615

As indicated on page one of the specification, all formulations of paroxetine sold prior to the instant invention, were formulated using an aqueous granulation process. In applicable part, applicant's invention relates to the surprising discovery that paroxetine tablets produced on a commercial scale under dry conditions exhibit properties that are different and superior to tablets made by wet granulation.

Applicants wish to cite the affidavits of Dr. Christopher T. Rhodes (of record, as being included in reference CAAA, a copy of which is enclosed herewith for the convenience of the Examiner) and Dr. Robin Roman (of record, as being included in reference CBBB, a copy of which is enclosed herewith for the convenience of the Examiner) in furtherance of the claimed invention. Dr. Roman was the director in charge of the development of paroxetine hydrochloride formulations from 1991 to 1993 and his affidavit outlines the detrimental effects of an intermittent pink hue that formed on commercial formulations of paroxetine prepared by the prior aqueous granulation process and the efforts expended to overcome it. As indicated in the Biography of Dr. Rhodes (also of record, as being included in reference CAAA, along with Dr. Rhodes Curriculum Vitae), Dr. Rhodes is a Professor of Applied Pharmaceutical Sciences at the University of Rhode Island. Professor Rhodes has published approximately two hundred and fifty publications on a variety of pharmaceutical topics associated with the design and evaluation of drug delivery systems and devices.

As indicated in paragraphs 6, 7 and 8 of Dr. Roman's affidavit, the pink hue problem cost SmithKline Beecham millions of dollars in lost revenue and potentially jeopardized the commercial viability of the product. Further, in paragraph 13 of his affidavit, Dr. Roman indicates that the improvements realized by changing the wet granulation process to a dry admixing and compressing process were highly unexpected. At that time, it was thought that because water was always present in the commercial process and the pink hue was only present in some of the batches, if water was the cause of the problem, the pink hue would appear in every batch. Dr. Roman concludes, at paragraph 15, that the instant invention saved time, money, resources and removed a major regulatory concern in the marketing of paroxetine.

Dr. Rhodes, at paragraphs 13 and 14 of his affidavit, describes the regulatory concerns posed by the pink hue and acknowledges that intermittent stability problems in the context of tablet formulation, such as the pink hue problem experienced with paroxetine, is one of the most difficult to solve. At paragraph 17, he states that reduction of water in the paroxetine manufacturing process would be one of the last factors he, as well as others skilled in the art, would have considered. And

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he found it a surprising and unexpected discovery that the intermittent pink discoloration was significantly decreased by changing the tableting formulation from wet granulation to dry admixing and compressing. At paragraphs 29, 30 and 32, Dr. Rhodes discusses the different and identifiable physical characteristics that result when tablets are prepared by wet granulation and when they are prepared by dry admixing and compression. Moreover, with regard to paroxetine, Dr. Rhodes concludes in paragraph 32 that the paroxetine tablets prepared by the dry admixing and compression process are superior to tablets made by wet granulation, because the dry admixed and compressed paroxetine tablets are less likely to develop an undesirable pink hue.

In view of the above, applicants contend that it was highly unexpected to discover that the intermittent pink hue problem was ameliorated by removing water from the processing procedure, when water was used in the preparation of all formulations of paroxetine sold at that time. And, as indicated in paragraphs 29 and 32 of Dr. Rhodes' affidavit, that tablets made by the dry process have different and superior properties to the tablets made by a conventional wet process.

If any matters remain to be resolved before search, examination and allowance, or if discussion of any matter will facilitate the prosecution of this application, the Examiner is invited to call the undersigned attorney at the number indicated below.

Respectfully submitted,



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Enclosures: Affidavit of Dr. Rhodes
Affidavit of Dr. Roman

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